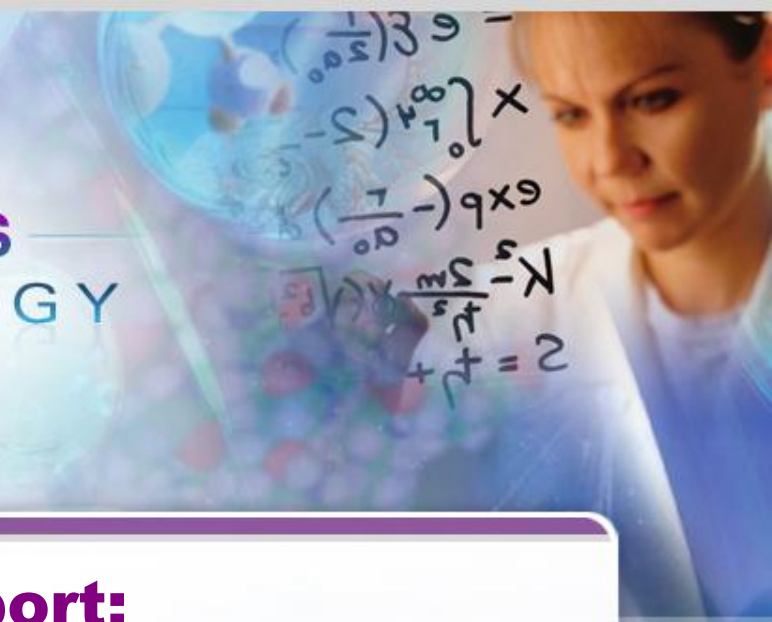
National Cancer Institute

PHYSICAL SCIENCES in ONCOLOGY



Status Report: Physical Sciences-Oncology Centers (PS-OC) Program

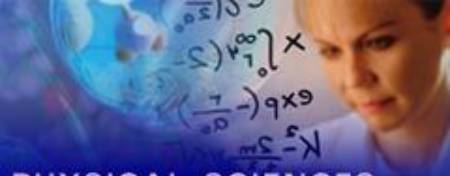
Larry A. Nagahara

Board of Scientific Advisors, November 7, 2013

Physical Sciences-Oncology Centers (PS-OC) Program: Premise

- Physical scientists have a history of contributing to cancer research (notably with advanced tools); however, they have faired less well in receiving grants where concepts from these disciplines are applied.
  - ***Advanced Tools: Proton Beam Therapy, MRI/PET/CT Imaging***
  - ***Concepts: Graph/Network Theory; Bayes' Theorem***
- Nascent concepts/ideas often take many years to establish and still more years to become "mainstream".
- Jerome Cornfield and team brought the concept of Bayesian methods, used more commonly by the information (encryption) community a decade earlier (1940's), to answer the following question:
  - **What's the probability that someone would develop lung cancer, given that he/she was/is a smoker?**
  - JNCI 1951, JNCI 1959, Surgeon General 1964

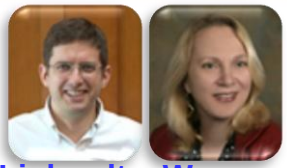
Physical Sciences-Oncology Centers (PS-OC) Program: Premise



- Center/Network approach implemented for the PS-OC Program to **accelerate the adoption ("learning curve") of concepts and advanced tools from the physical sciences** that can be shared more readily with other investigators in the center/network and beyond.
- Increases cross-section for impact (*e.g.,* new insights) by **conjoining teams of physical scientists and cancer researchers** that are focused on relevant questions and systems in cancer.
- Training/career development is a key component for **generating early adopters** of these concepts/tools.
- **Investigator-initiated center pilots/trans-network pilots** to further accelerate adoption and enhance integration between the two fields.

PS-OC Network (circa 2013): Physical scientists & cancer researchers integrated at the start

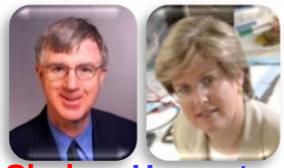
PHYSICAL SCIENCES in ONCOLOGY


Liphardt Weaver

Stanford


O'Halloran Licht

Northwestern


Shuler Hempstead

Cornell


Manalis Jacks

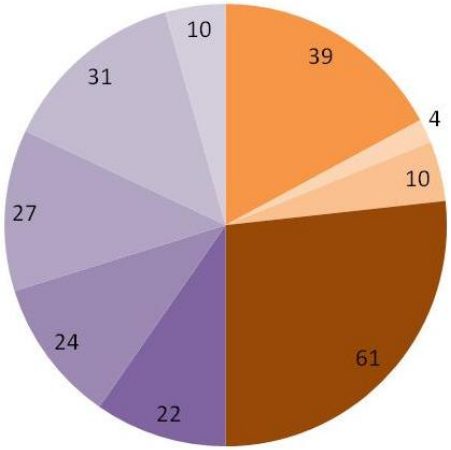
MIT


Hillis Agus

USC


Michor Holland

DFCI



Scripps

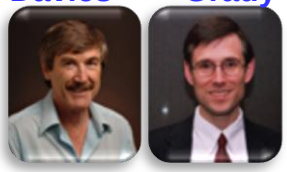
Kuhn Bethel

Princeton

Austin Tlsty

ASU

Davies Grady

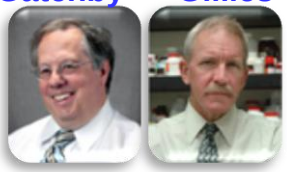


TMHRI

Ferrari Curley

Moffitt

Gatenby Gillies



Johns Hopkins

Wirtz Semenza

PI + SI

12 "Virtual" Centers

Over 110 Institutions:

- 83 Domestic
- 32 Foreign

corresponding to:

- 700+ investigators, collaborators, & advisors
- 600+ trainees (post-docs, graduate, & undergraduate)

participating in the PS-OC Network

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Cancer Problem: Many cancer patients develop resistance to therapy

What are the fundamental bases of rapid development of resistance?

Traditional View:

External stress + Microenvironment =

⇨ Selection of the fittest

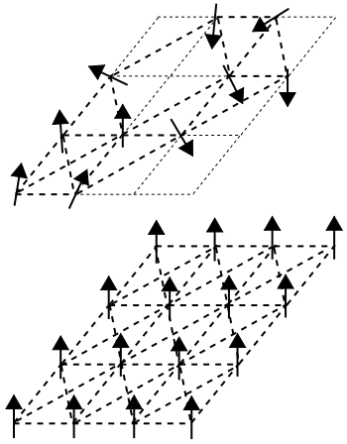
⇨ Development of resistance

Additional Physical Science Perspective:

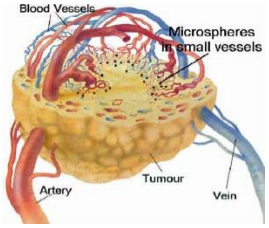
Spin glass model helps understand long-range interactions amongst weakly interacting parts.

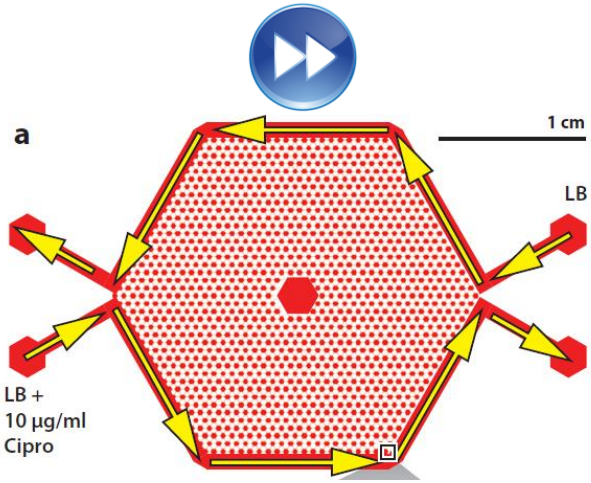
Spatially heterogeneous "micro-habitats" are critical to accelerated cell resistance.

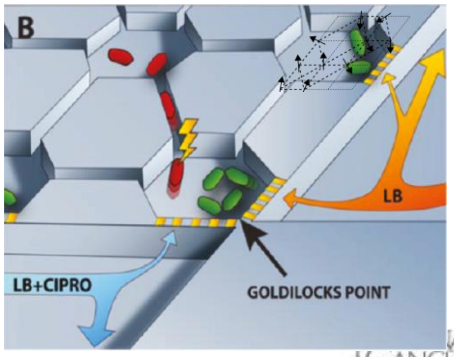
(Robert Austin, Princeton PS-OC) – Physics theory of spin glass is a general way to understand complex behavior which arises when weakly interacting agents exhibit "frustrations" – conflicting (multiple) choices/commands. Likewise, cancer cells have conflicting commands given to them by neighbors and are reflective of the phenotypic and genotypic complexity observed.



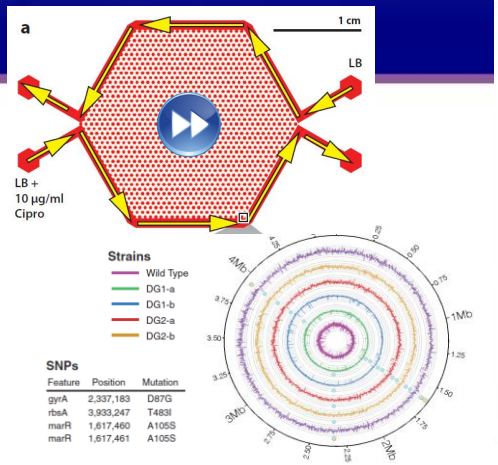
Spin Glass Analogy

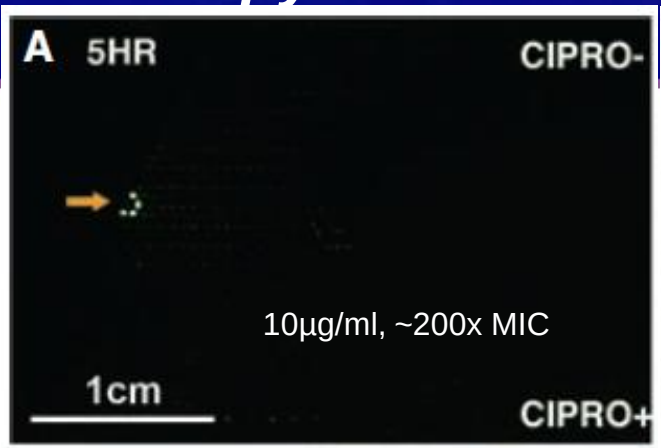


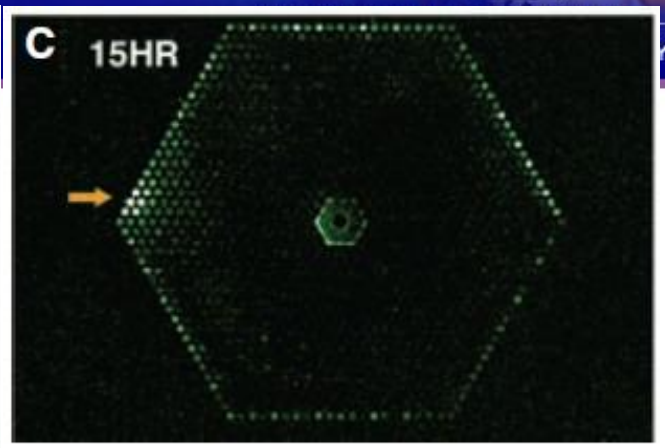




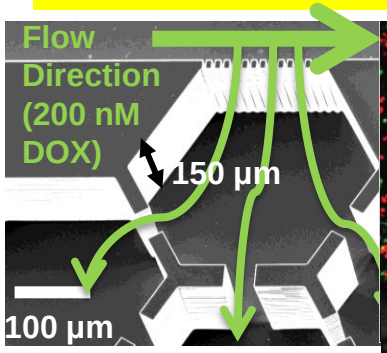
Cancer Problem: Many cancer patients develop resistance to therapy

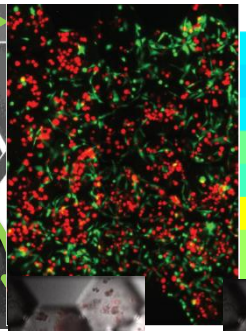


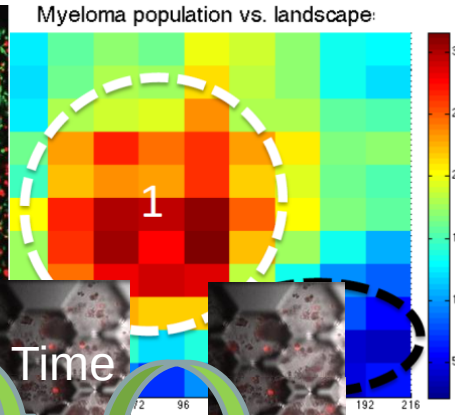


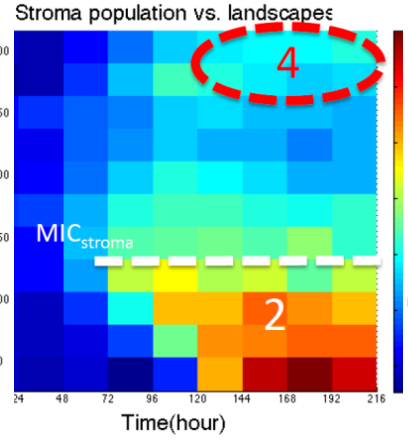


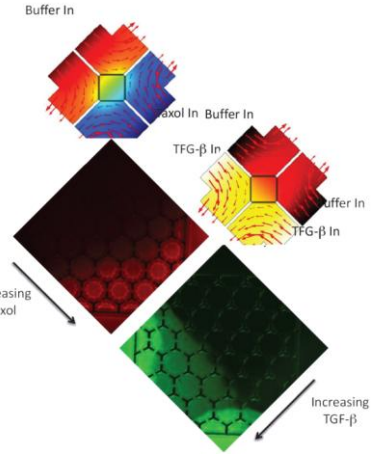
***Princeton's "Spin Glass" Model + "Fast-Forward" Tool: Intra-Center Project & Trans-Network Pilot* (Moffitt PS-OC) *Evolution of resistance in multiple myeloma in the microhabitat with drug gradients*.**











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Cancer Problem: Distinct parameters (genetic, anatomical, physical) are strongly associated with increased risk/poor outcomes

Why do so many different factors all matter so much to outcome?

Traditional View:

Certain genetic , physical, anatomical properties are known risk/outcome parameters for certain types of cancers.

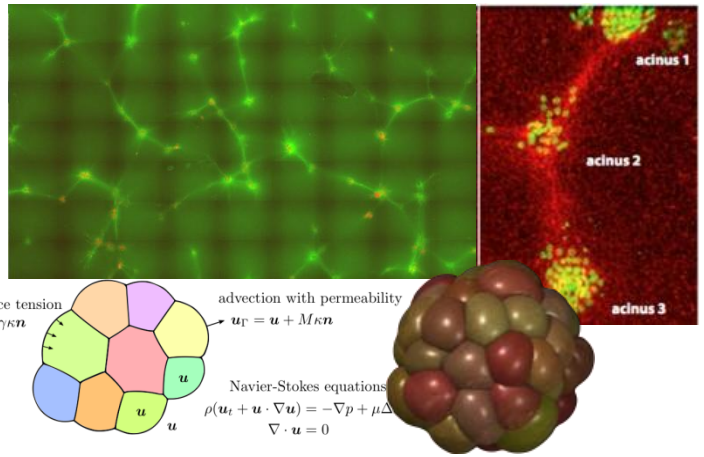
Loose association with each other.

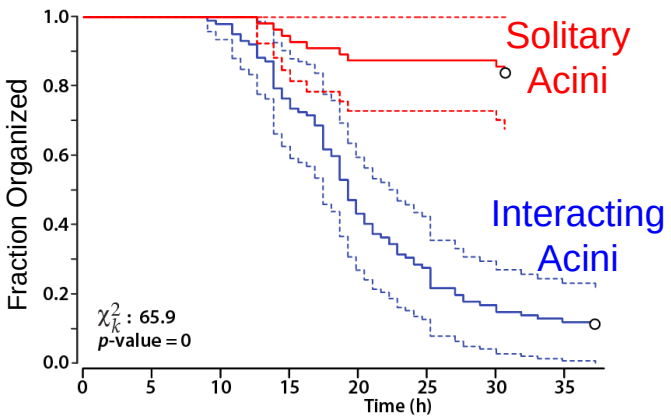
Additional Physical Science Perspective:

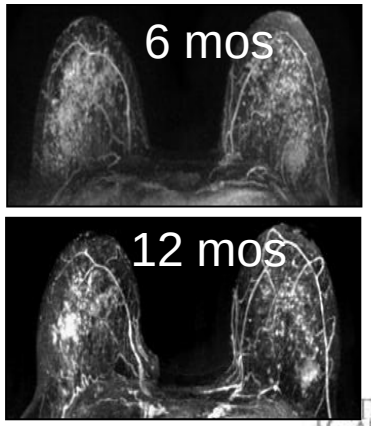
Groups of acini interact cooperatively to transition to an invasive phenotype.

This invasive phenotype may be controlled by tensile stress.

(Jan Liphardt, Stanford PS-OC) – Physicists, cancer researchers, and mathematicians used Ras-transformed mammary acini to investigate the physical interactions and **mechanical cooperativity** over long distances that indicate the transition/progression to a malignant phenotype is a **collective phenomenon**. **Invented first principles multiphysics algorithm** for 3D cell-tissue mechanics computational model. Currently, conducting a pilot project on the biophysical properties of a collagen a risk factors for developing 'silent' breast cancers







Pilot project: biophysical factor of 'silent' cancer in AA women.

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Collaborative and Scientific Output

PS-OC Program FY'09 – present:

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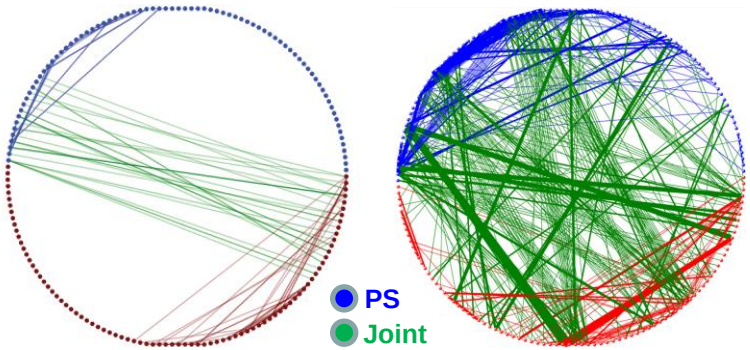
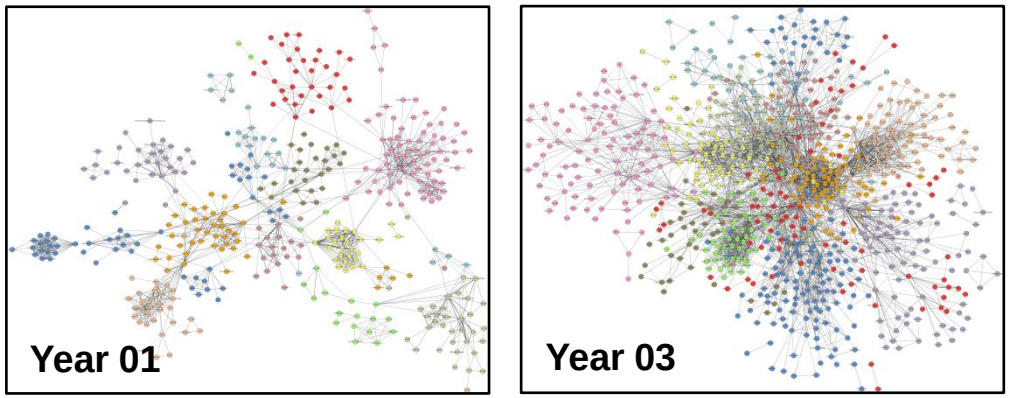
Increase in Transdisciplinary Authorship Compared to Pre-Award Years



Pre-Award 2006-2008

PS-OC Years 2010-2012

More Than 2-Fold Increase in Interactions* Resulting in a Further Integrated Network



* Interactions (reported by investigators in progress report): joint publication, on-going collaboration (exchange material, students, etc.)

- ***Advanced Tools:** Xiaolin Nan & Frank McCormick (UCB PS-OC): Super resolution imaging reveals dimerization-dependent Ras/Raf signaling – PNAS (2013) (doi:10.1073/pnas.1318188110)*
- ***Concepts:** Alexander van Oudenaarden, Hans Clevers, & Tyler Jacks (MIT PS-OC): Apply the concept of control theory and statistical physics to predict optimality in intestinal crypt development – Cell 148, 608 (2012)*

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Lessons from the Phage Treaty

How do I culture better interactions between physical scientists and cancer researchers…

- **"helped many physicists make the transition to biology"**
- **They encouraged other investigators in the field to concentrate on seven bacteriophages ... That way, experimental results from different laboratories could be compared.**

(Standarization)

calteches.library.caltech.edu/584/02/
Ann. Rev. Genet 1982. 16:501-05

Collective Insights of Physical Science Parameters: "Living Project"

PHYSICAL SCIENCES in ONCOLOGY

SCIENTIFIC REPORTS | 3 : 1449 | DOI: 10.1038/srep01449

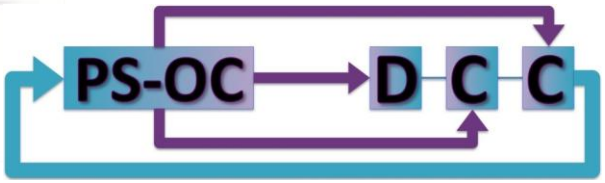
A physical sciences network characterization of non-tumorigenic and metastatic cells

The Physical Sciences - Oncology Centers Network*

- First large-scale, comprehensive, biophysical examination of identical cells
  - 17 Institutions
  - 20 Labs
  - 24 Techniques/approaches
- Combined analysis through Data Jamboree

- Continued as a "Living Project" through repository and database
- Raw data (published/ unpublished) for additional analysis
- Request for additional characterization (data upload required post-publication)

PS-OC Network Bioresource Core Facility



http://opso.cancer.gov/data/

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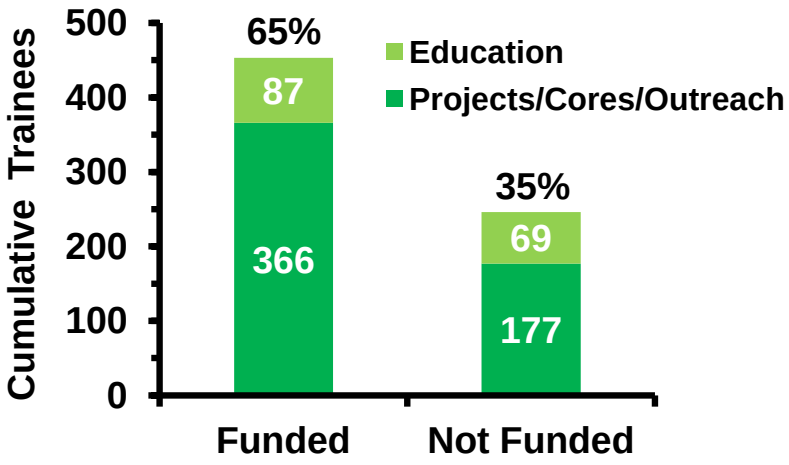
Training & Pilot Projects Output

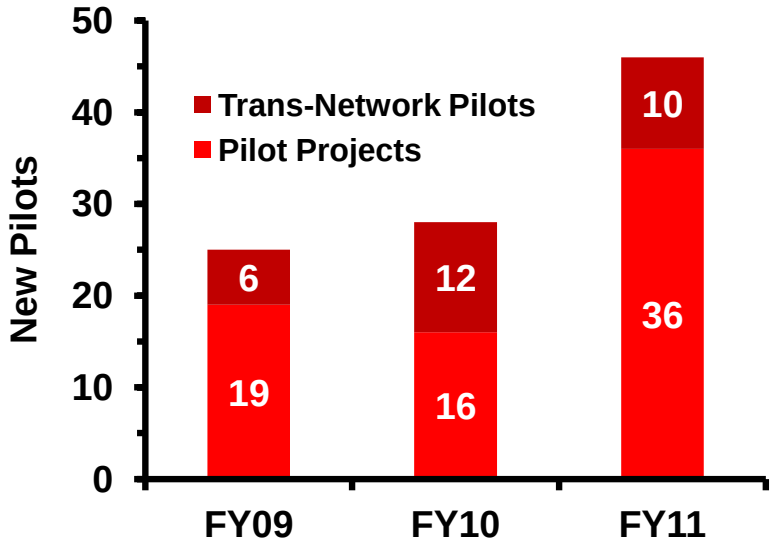
Various Components Provide Flexibility to Investigators

Network Supported ~ 450 Trainees and a Range of Training Opportunities



- Training is a key component for **generating early adopters** of these concepts.

Network Added ~100 Exploratory Studies



- **Investigator-initiated center pilots/trans-network pilots** to accelerate adoption and enhance integration between the two fields

Physical Sciences-Oncology Centers (PS-OC) Program PAR Request

OPSO staff discussions with:

- ❖ Other PAR programs w/ network
  - ❑ NIOSH Agriculture Disease Centers (U54) – PO: Allen Robinson
  - ❑ Quantitative Imaging Network (QIN: U01) – PO: Larry Clarke/Robert Nordstrom
  - ❑ Specialized Programs of Research Excellence (SPORE: P50) – PO: Toby Hecht
- ❖ Program Evaluations
- ❖ PS-OC Implementation Team

Issuances of PS-OC Program (PAR)

- **2 Themes (suggested):**
  - **The Physical Dynamics of Cancer**
  - **Spatial Organization and Cancer**
- **Competition under Type 1**
- **U54 mechanism up to $1.5M (DC)/year – center (5 years max.)**
  - **2-3 Projects/Center**
  - **Education/Training Unit**
  - **Pilot/Trans-Network Projects**
- **Two receipt dates per year for 3 years, except FY'14 having only one receipt date**

PS-OC PAR Suggested Thematic Areas

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Based on:

1) **Inputs from scientific workshops (75% external to PS-OC Program);**
2) **Scientific advances from program;**
3) **Portfolio analysis of NCI portfolio;**
4) **NCI program leaders**

The Physical Dynamics of Cancer

- ***Overview:*** ***Physical properties such as bioelectric signals, transport phenomena, mechanical cues, and thermal fluctuations*** may regulate (+/-) the initiation and progression of cancer.
- ***Relevant Physical Science Approaches:*** Precision measurements on single-cells and bulk samples, high-dimensional analysis, computational physics

Spatio-Temporal Organization and Information Transfer in Cancer

- ***Overview:*** ***Organization of structures across all length scales (e.g., subcellular, cell, tissue, organ) and time scales*** is required for maintaining the transfer of information that is critical for controlled growth.
- ***Relevant Physical Science Approaches:*** Advanced imaging and measurements, tissue mimetic and engineering, computational physics

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PS-OC PAR Implementation Team

NCI DOC Members

- CCT: Jonathan Wiest
- CRCHD: Alison Lin
- DCB: Dan Gallahan
- DCCPS: Mukesh Verma
- DCP: Nada Vydelingum
- DCTD: John (Kim) Jessup
- OPSO: Sean Hanlon

Extensive role of the Implementation Team:

- Provide programmatic suggestions and insights in preparing the PAR
- Assist in pre-application, application, post-review, and pre-award activities;
- Communicate and gather PS-OC-relevant information to your DOC's program staff in a timely fashion, as appropriate;
- Identification of a suitable DOC program official (PO) and/or project scientist (PS).

Diversification of Potential Applicants

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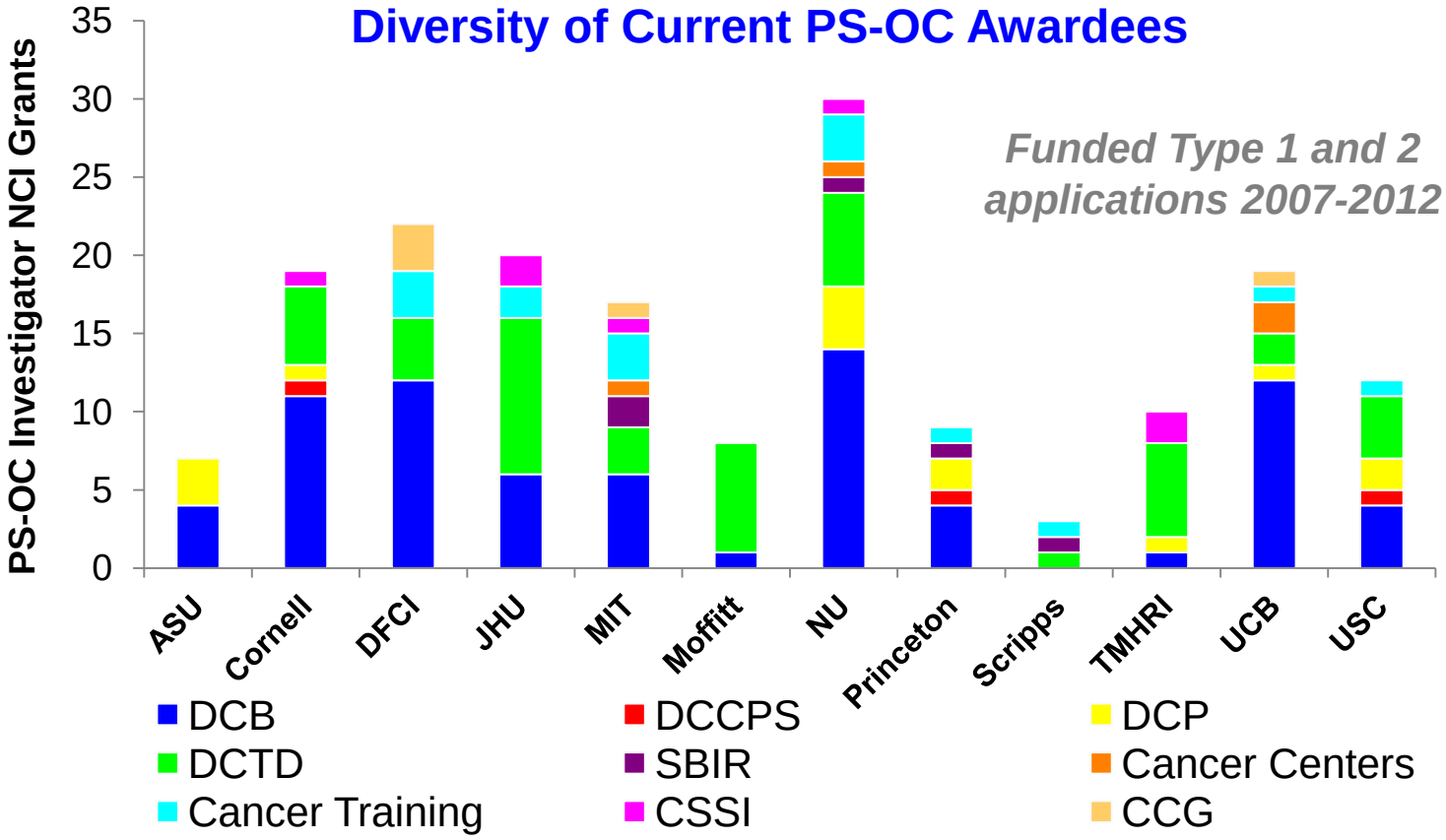
- Letter on Intent (LOI) to be due 6-8 weeks before application is due
- In case a DOC would like to hold the grant, ample time is allotted to obtain DOC approval with their respective director.



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Proposed PS-OC PAR Program FY'14-FY'16:

Organization and Process

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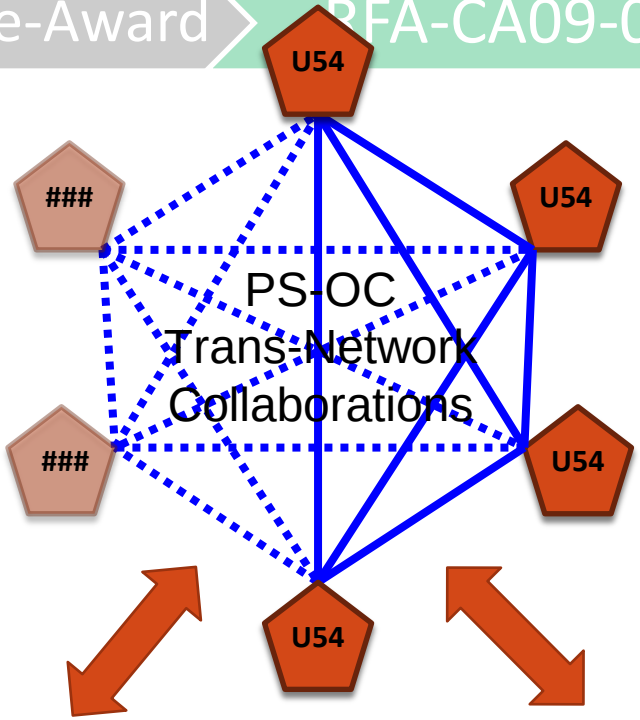
FY09 ★**FY14** **FY16**

Pre-Award | RFA-CA09-009 | **PS-OC Network PAR** | Future



NCI Staff

CCT CRCHD DCB

DCCPS DCP DCTD

OPSO ··· (project scientists)

Scientific Focus Group

Outstanding (physician)scientists to help advise/guide the program.

Issuances of PS-OC Program (PAR)

- 2 Themes (suggested):
  - The Physical Dynamics of Cancer
  - Spatial Organization and Cancer
- Competitive Direct [illegible]
- U54 Mechanism up to $1.5M (DC)/year – center (5 years max.)
  - 2-3 Projects/Center
  - Education/Training Unit
  - Pilot/Trans-Network Projects
- Two receipt dates per year for 3 years, except FY'14 having only one receipt date

"Bring the physics, not just the physicist, to biology"…oncology

OPSO Team

PHYSICAL SCIENCES in ONCOLOGY

Mariam Eljanne, PhD
Project Manager

Michael G. Espey, PhD
Project Manager

Jonathan Franca-Koh, PhD
Project Manager

Sean E. Hanlon, PhD
Project Manager

Nastaran Z. Kuhn, PhD
Project Manager

Nicole M. Moore, ScD
Project Manager

Teresa K. Schuessler, MS
Health Communications Fellow

Katrina I. Theisz, MS
Operations Coordinator

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Thanks!
Questions?

Backup Slides

NCI-OPSO/NSF-ENG & MPS Joint Collaborations:

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Physical and LIfe Sciences Early Research (PLIER) Awards

Physical and Engineering Sciences in Oncology (PESO)

PROGRAM ANNOUNCEMENT
NSF 12-514

National Science Foundation

Directorate for Engineering **(ENG)**
- Division of Civil, Mechanical and Manufacturing Innovation
- Division of Electrical, Communications and Cyber Systems
- Division of Chemical, Bioengineering, Environmental, and Transport Systems

Directorate for Mathematical & Physical Sciences **(MPS)**
- Division of Materials Research

National Cancer Institute

	Leverage Funding	*Total Funds*
2011: 6 Awards	*~3:1*	*$2.6 M*
2012: 6 Awards	*>3:1*	*$3.2 M*

NSF-MPS Workshops

November 1-2 2010

Physics of Cancer Metastasis

November 13-14 2012

Theoretical Foundations of Drug and Immune Resistance in Cancer

November 5-6 2013

Physical Principles of Human Cancer Imaging

Cancer Problem: RAS-RAF-MAPK pathway is abnormally activated many cancers

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How does the spatial organization of signaling pathways modulate function?

Traditional View:

Immunoprecipitation and crystalography experiments suggest a role for multimerization of RAF in activation of the pathway

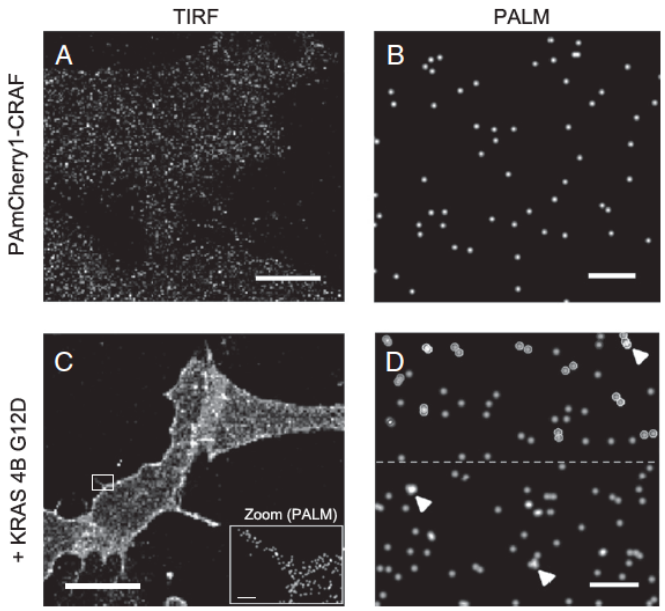
The degree and location of multimerization are currently unknown.

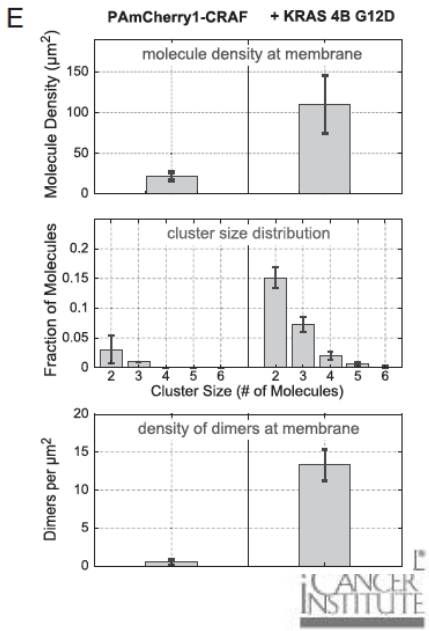
Additional Physical Science Perspective:

PALM and spatial analysis techniques allow high precision spatial and stoichiometric analysis of single molecules in intact cells.

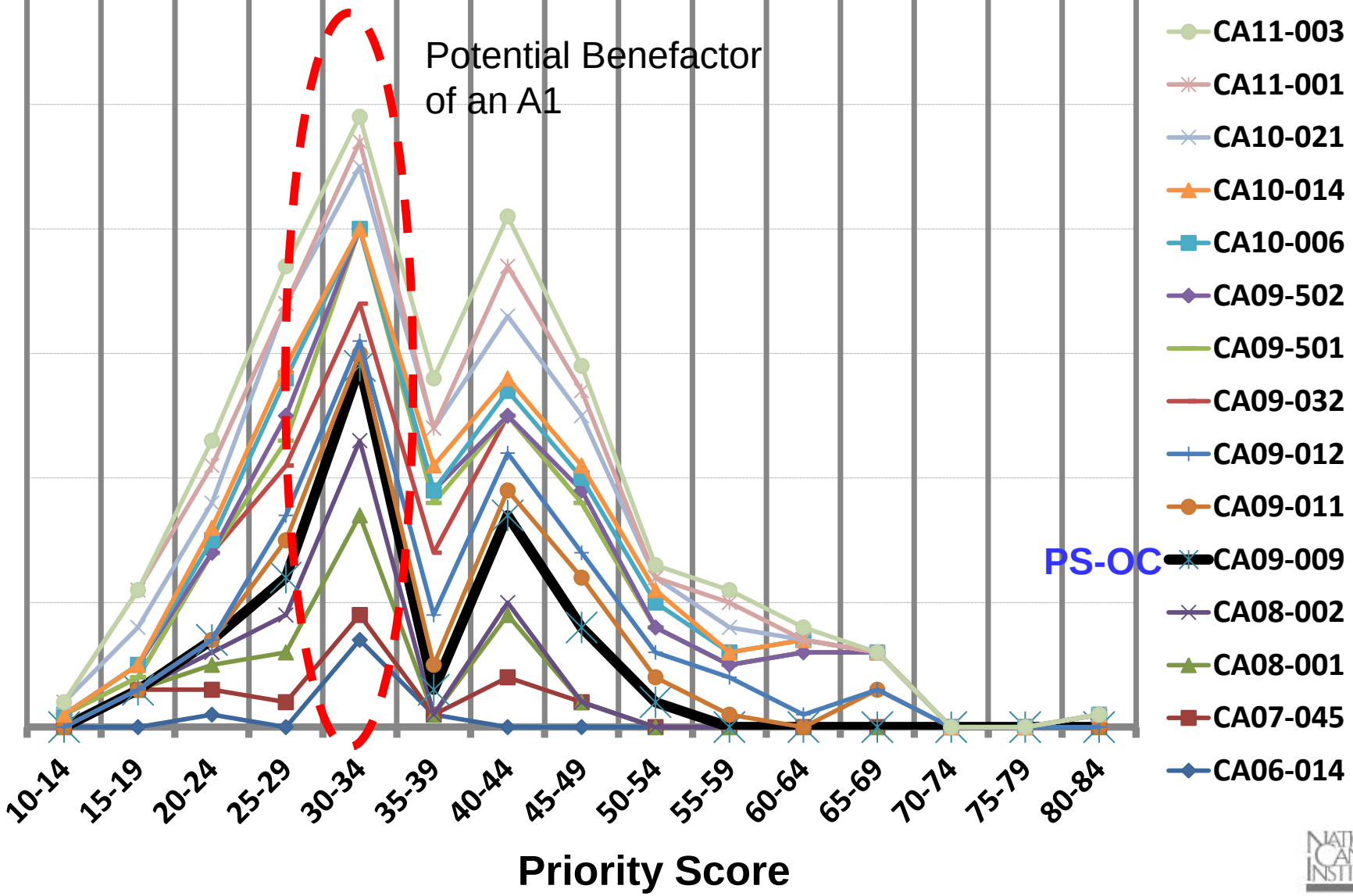
Show that CRAF forms dimers and multimers at the cell surface under activating conditions.

Xiaolin Nan/Steve Chu and Frank McCormick Stanford PS-OC – Photoactivated localization microscopy (PALM) combined with computer simulations and spatial analysis techniques allows high precision protein localization and stoichiometric analysis through directly visualization of CRAF multimers under activating conditions.





Bimodal Distribution: U54 Mechanisms



APHELION – A Study by the World Technology Evaluation Center (WTEC)

- **APHELION**: Assessment of Physical Sciences and Engineering Advances in Life Sciences and Oncology
- **Goal**: To determine the status and trends of research and development whereby physical sciences and engineering principles are being applied to cancer research, oncology, and other biomedical research areas in leading laboratories and organizations via an on-site peer review process in Europe and Asia.

http://www.wtec.org/aphelion

APHELION - Distinguished Panelists and Advisors

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Expert panel

- Chair: Paul Janmey, UPenn
- Dan Fletcher, UCB
- Sharon Gerecht, JHU
- Parag Mallick, Stanford
- Owen McCarty, OHSU
- Lance Munn, Harvard
- Cindy Reinhart-King, Cornell

Advisors

- Tito Fojo, NCI
- Denis Wirtz, JHU


Paul

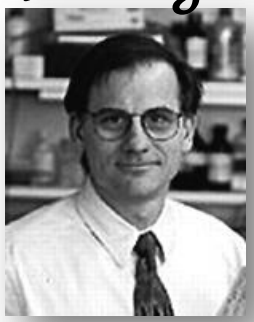

Dan


Sharon


Parag


Owen


Lance


Cindy


Denis

APHELION

http://www.wtec.org/aphelion

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APHELION Europe Sites (25) Visited

http://wtec.org/aphelion/index.php

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FRANCE
- Institute Curie, Paris
- University of Paris Diderot

GERMANY
- Dresden Technical University
- Gottingen University
- Max Planck Institute (Dresden, Gottingen)
- Technical University of Munich
- University of Heidelberg
- University of Leipzig
- University of Rostock

ISRAEL
- Technion University
- Weizmann Institute

ITALY
- European Institute of Oncology
- University of Milan
- University of Padua

SWEDEN
- The Karolinksa Institute
- The Royal Institute of Technology
- Uppsala University

The NETHERLANDS
- Hubrecht Institute, Utrecht
- Radboud University Nijmegen
- The University of Leiden

SPAIN
- University of Barcelona
- University of Basque Country

SWITZERLAND
- Ecole Polytechnique Federal de Lausanne (EPFL)
- University of Basel

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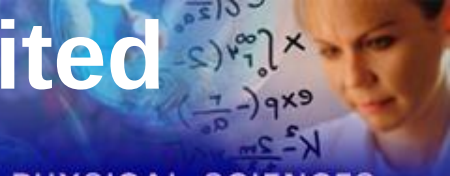
APHELION Asia Sites (20) Visited

http://wtec.org/aphelion/index.php



CHINA

- East China University of Science and Technology
- Beijing Tumor Hospital
- Beijing University Medical Center
- Center for Theoretical Biology, Peking University
- Department of Biomedical Engineering, Peking University
- Institute of Physics, CAS

HONG KONG

- Centre for Cancer Research, University of Hong Kong
- Center for Quantitative Systems, Hong Kong Baptist University
- Institute for Computational and Theoretical Studies

JAPAN

- Center for Developmental Biology, RIKEN
- Center for iPS Cell Research and Application, Kyoto University
- Immunology Frontier Research Center, Osaka University
- Laboratory for Cellular Systems Modeling, RIKEN Yokohama
- Laboratory of Bioimaging and Cell Signaling, Kyoto University

SINGAPORE

- Cancer Science Institute, NUS
- Centre for BioImaging Sciences, NUS
- Institute of Molecular Biology, A*Star
- Mechanobiology Institute, NUS
- Nanyang Technological University

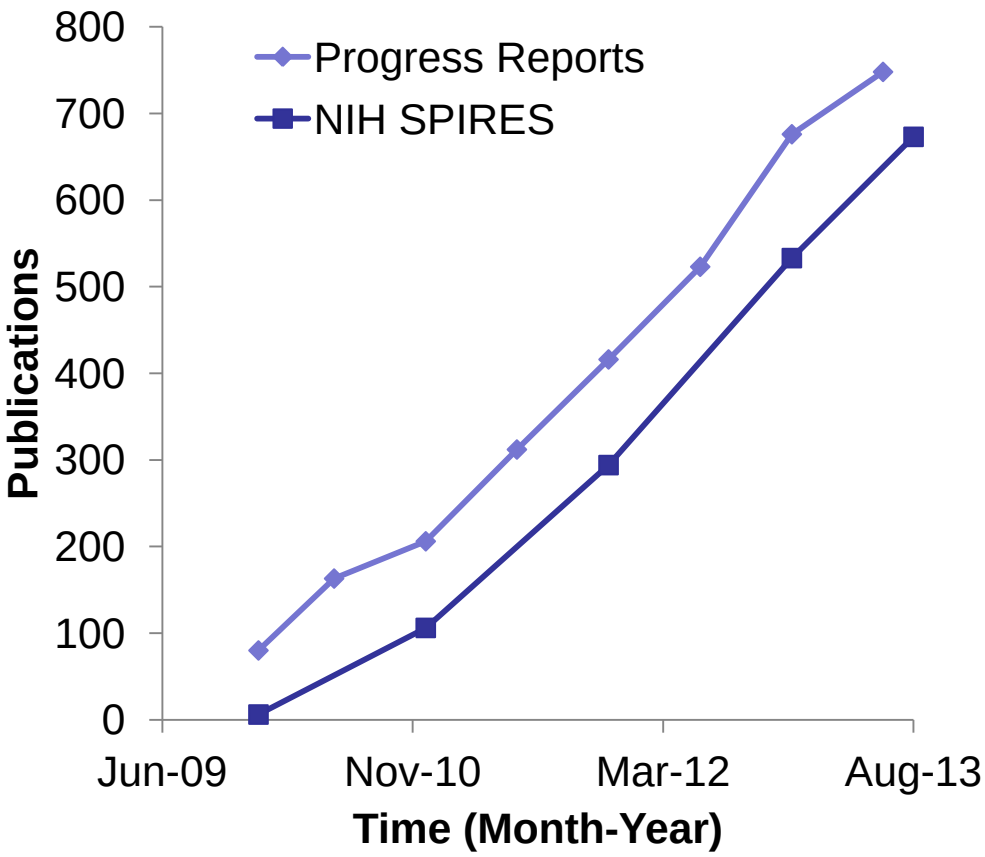
TAIWAN

- Institute of Biological Chemistry, Academia Sinica

Publication Statistics

June 2013

PHYSICAL SCIENCES in ONCOLOGY



Total # of Pubs……..748
Average Impact Factor…….. 9.31
Average first year citations……...6.21
Number of Journals…….. 273

Most Frequent Journals

Journal	# of Pubs	Journal Impact Factor
PNAS	39	9.66
PLoS One	38	4.20
Cancer Research	25	7.90
Physical Biology	24	2.60
Blood	17	10.18
Cell	16	32.33
Nature	16	35.90
Biophysical journal	11	3.86
Nucleic Acids Research	11	7.96
Biomaterials	10	7.45
Nature Biotechnology	10	26.24
Frontiers in Oncology	10	0.00

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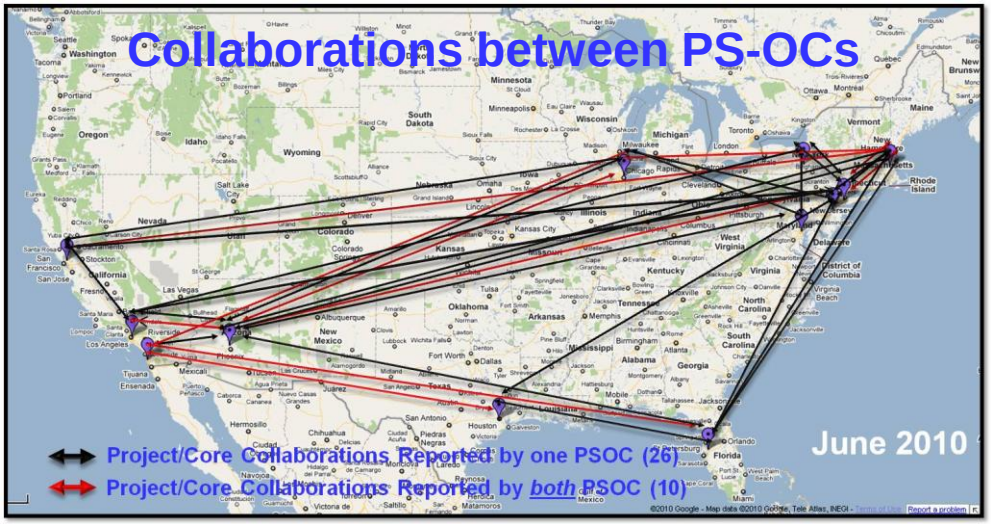
Collaborative and Scientific Output

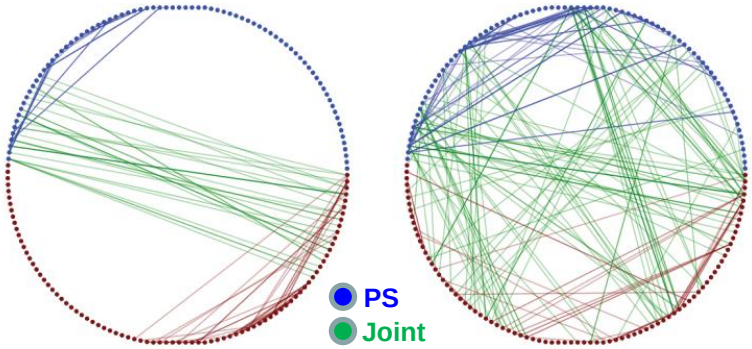
PS-OC Program FY'09 – present:

PHYSICAL SCIENCES in ONCOLOGY

interdisciplinary iTRAQR
TEAM REPORTING, ANALYSIS, AND QUERY RESOURCE



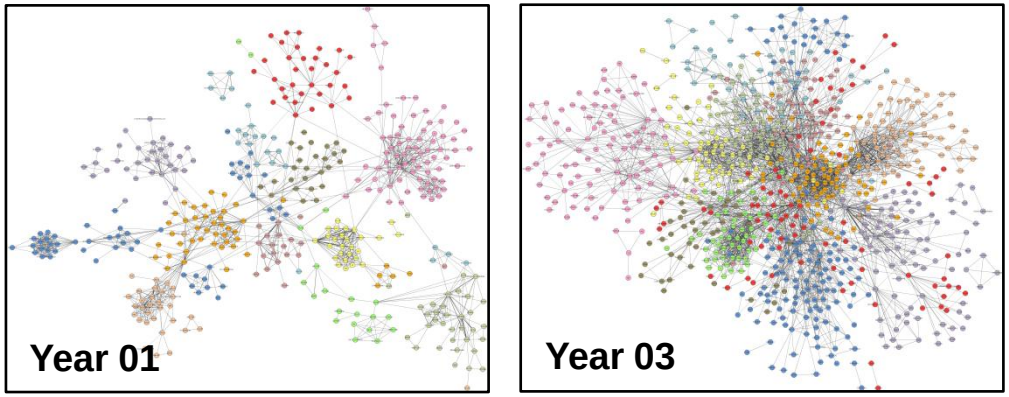
Increase in Transdisciplinary Authorship Compared to Pre-Award Years



Pre-Award 2006-2008

PS-OC Years 2010-2012

More Than 2-Fold Increase in Interactions* Resulting in a Further Integrated Network



* Interactions (reported by investigators in progress report): joint publication, on-going collaboration (exchange material, students, etc.)

Collective Insights of Physical Science Parameters: "Living Project"

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